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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/702,283	10/30/2000	Benjamin Oshlack	200.1116US	1434

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EXAMINER	
CELSA, BENNETT M	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 01/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/702,283	OSHLACK ET AL.	
	Examiner	Art Unit	
	Bennett Celsa	1639	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see attached discussion.*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *1-3 and 5-38*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

Bennett Celsa
Primary Examiner
Art Unit: 1639

DETAILED ACTION

Advisory Action Cont.

Applicant's after-final response date 12/22/03 is acknowledged.

Arguments presented therein were considered but deemed nonpersuasive for the following reasons. The prior rejections are reproduced for applicant's convenience.

Outstanding Objection(s) and/or Rejection (s)

1. Claims 1-3 and 5-38 are rejected under 35 U.S.C. 102(a,b,e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Oshlack et al. US Pat. No. 5,639,476 (6/97). The presently claimed invention is directed to: controlled release oral dosage forms (e.g. tablets, capsule) comprising:

hydrocodone (or pharmaceutical salts) AND

"controlled release material to render said dosage form suitable for twice-a-day administration to a human patient ... said dosage form providing a therapeutic effect for at least 12 hours". Preferred suitable "controlled release materials" include ammonio-methacrylate copolymers of acrylic/methacrylic acid esters having low content of quaternary ammonium groups (e.g. Eudragit RS and/or /RL as the "controlled release material" as disclosed in elected Example 3). The hydrocodone may be dispersed in a (multiparticulate) matrix in which the multiparticles are disposed in a pharmaceutically acceptable capsule (e.g. see claims 2, 3 and 5).

The presently claimed compositions result in *various pharmacologic parameters* including:

a. " C12/Cmax ratio of 0.55 to 0.85" (E.g. claims 1, 36, 37);

b. "Plasma concentration of hydrocodone of at least 8 ngm/ml at from about 2 to about 8 hours after administration ... a dosage form containing 15mg hydrocloride bitartrate" (E.g. See dependent claims 14-15);

c. " *mean* C12/Cmax ratio of 0.55 to 0.85" (E.g. claim 38);

d. "rate of absorption during the time period from Tmax to about 12 hours after oral administration ... from about 55% to about 85% of the rate of elimination during the same time period" (E.g. claim 31);

e. "providing a Tmax of hydrocodone in-vivo at from about 2 to about 8 hours" and "providing a C12/Cmax ratio of 0.55 to 0.85" (E.g. see claim 32: see also Tmax values in dependent claims 11-13). See also dependent claims 27-30 for more Tmax parameters;

f. "after a first administration providing a Cmax of hydrocodone which is less than about 50% of the Cmax of an equivalent dose of an immediate release hydrocodone reference formulation" (E.g. see claim 33; dependent claims 16-17);

g. "after a first administration providing a time to 80% mean Cmax which is about 90% to about 110% of the time to 80% mean Cmax of an equivalent dose of an immediate release hydrocodone reference formulation" (E.g. see claim 34; dependent claim18); or "80% mean Cmax of hydrocodone from about .5 to about 1.5 hours (e.g. see dependent claim 19: see also dependent claims 21-26 for variations thereof; "a 90% mean Cmax which is about 150% to about 250% of the time to 90% Cmax of an equivalent dose of immediate release hydrocodone reference formulation" (e.g. see dependent claim 20);

"a 90% mean Cmax of hydrocodone from about 1.5 to about 2.5 hours" (and variations thereof: see e.g. dependent claims 21--22)

h. "Tmax of about 2 mg/hr to about 4 mg/hr", "a mean in-vivo absorption rate from Tmax to about 12 hours after administration which is from about 0.08 mg/hr to about 0.4 mg/hr" ... "based on oral administration of a dosage form containing 15mg hydrocodone bitartrate". (E.g. see claim 35);

I. "An in vitro release of at least 18% to about 42.5% by weight of the hydrocodone or salt from the dosage form at one hour ... " (E.g. see claim 7);

j. "Dissolution rate in vitro" (determined by USP Paddle/Basket method at 100 rmp in 900 ml aqueous buffer at a pH of 1.2 or 7.5 at 37 degrees celsius) of:

from about 25 to about 65% ... after 2hrs;

from about 45 to about 85% ... after 4hrs; and

greater than about 60% ... after 8 hrs (See E.g. dependent claims 7-10), respectively).

The Oshlack et al. Patent reference teaches controlled release oral dosage forms (e.g. tablets, capsule) comprising:

OPIOID analgesics (or pharmaceutical salts: e.g. see patent claims 1 and 6)

AND

"controlled release material to render said dosage form suitable for twice-a-day administration to a human patient e.g. "said dosage form providing a therapeutic effect for at least 12 hours" (e.g. see patent claim 3). Oshlac et al. teach "controlled release materials" within the scope of the presently claimed invention which include ammonio-methacrylate copolymers of acrylic/methacrylic acid esters having low content of

quaternary ammonium groups. E.g. patent claim 1; col. 4-5; 7-12 with Eudragit RS and/or /RL as the "controlled release material" being most preferred (e.g. see col. 9 ; and patent examples). . The opioid analgesic may be dispersed in a (multiparticulate) matrix in which the multiparticles are disposed in a pharmaceutically acceptable capsule (e.g. examples; patent claim 4). The Oshlack et al. Teaching of opioid analgesics as the most preferred active agent (e.g. see examples and patent claims) with the preferred opioid analgesics comprising less than 15 members, one of which is hydrocodone (e.g. see paten claim 6) would render the selection of hydrocodone by one of ordinary skill in the art immediately envisaged (e.g. anticipates), or alteratively obvious; thus arriving at compositions containing ingredients within the scope of the presently claimed invention. E.g. see See *In re Schaumann*, 572 F.2d 312. 197 USPQ 5 (CCPA 1978); MPEP 2131.02. The Oshlack et al. reference compositions further discloses controlled release profiles (e.g. see col 4, particularly lines 40-60; col. 11-12; alterable by changing resin concentrations see col. 10 and 13); and methods of manufacture (e.g. of multiparticles: col. 13-16) which are clearly within the scope of the presently claimed invention (e.g. compare with present specification).

Accordingly, the Oshlack et al. reference anticipates or alternatively renders obvious compositions (and methods of making and use) within the scope of the presently claimed invention; in which the resulting compositions MUST *inherently* possess *the various pharmacologic parameters (e.g. a. to j. Above)* as presently claimed. The patent office lacks the necessary facilities to make comparisons between prior art and presently claimed compositions.

Discussion

Applicant's arguments directed to the above prior art rejection were considered but deemed nonpersuasive for the following reasons.

Applicant argues that Oshlack et al. fail to teach or suggest pharmacokinetic parameters with respect to dosage forms containing hydrocodone or a pharmaceutically acceptable salt thereof as recited in the present claims

This argument was considered but deemed nonpersuasive for the reasons recited in the above rejection e.g. Oshlack et al. teach controlled release formulation components suitable for a twice a day formulation of active agents (e.g. including hydrocodone), and means of altering these components (if necessary), to arrive at a composition that possesses (e.g. inherently) the presently claimed pharmacokinetic parameters.

Applicant further argues that "Oshlack et al. fail ... to teach ... or suggest" a dosage form hydrocodone or a pharmaceutically acceptable salt thereof suitable for twice a day administration comprising C12/Cmax ratio of 0.55 to 0.85.

This argument was considered but deemed nonpersuasive since the Oshlack reference clearly suggests hydrocodone or a pharmaceutically acceptable salt thereof suitable for twice a day administration (e.g see patent claims especially claims 1, 3, 6, 10-13 directed to twice a day hydrocodone controlled release dosage forms) with a teaching as to the use of a controlled release formulation, containing ingredients within the scope of applicants claims, which can be manipulated, if necessary, to achieve a twice a day formulation; and thus arrive at compositions which would necessarily

possess (e.g. inherently) the presently claimed pharmacokinetic parameters (e.g C12/Cmax ratio of 0.55 to 0.85).

Applicant argues that one of ordinary skill in the art would look toward MS CONTIN since "MS CONTIN is the only formulation described in the Examples of Oshlack et al. which could be related to the formulations of the present invention" since it is "a known 12 hour opioid formulation suitable for twice a day administration". Using Examples 19-20, Table 26 and Fig. 8 applicant calculates a C12/Cmax ratio of 0.16 which is outside that presently claimed.

Applicant's argument is nonpersuasive for several reasons.

First, Oshlack et al. use MS CONTIN for purposes of comparing the Oshlack's improved compositions to that of the prior art. Accordingly, MS CONTIN is NOT representative of the Oshlack reference compositions and one of ordinary skill in the art would not look to MS CONTIN if one wished to practice THE OSHLACK disclosed or CLAIMED INVENTION.

In fact one of ordinary skill in the art would look to the Oshlack disclosure as described in the above rejection. The Oshlack disclosure (including the examples) teaches obtaining a "desired therapeutic effect for **about 12 hours** (emphasis provided) to about 24 hours" (e.g. see col. 5, especially lines 5-15) by utilizing "controlled release coatings" which comprise "Hydrophobic acrylic polymers" which preferably include "Eudragit RL/RS"; with the desired release profile being easily obtained by "changing the relative amounts of different acrylic resin lacquers included in the coating" (e.g. see col. 9-10). Additionally, optimal dissolution profiling can be obtained by "increasing or decreasing

coating thickness. ..", "altering the manner in which the plasticizer is added... " (e.g. see col. 13). Accordingly, the reference teaches one of ordinary skill in the art how to make the Oshlack disclosed and claimed hydrocodone formulations suitable for twice-a-day administration. Accordingly, one of ordinary skill would not turn to MS CONTIN for determining a twice a day formulation since it is a less desirable prior art formulation (e.g. MS CONTIN); and more importantly is clearly outside of the scope of the Oshlack patent claims. Interestingly, applicant's argument fails to indicate what compositional feature (e.g. coating components and proportional amounts, if present) would motivate one of ordinary skill in the art to consider MS CONTIN in the context of the OSHLACK et al. disclosed and claimed invention.

Additionally, it is further noted that *applicant has failed to attempt* to calculate any C12/Cmax (or other pharmocological parameters) for any of the Oshalck et al. exemplified embodiments. It would appear to the examiner that the examples would be more instructive to one of ordinary skill in the art as to how to make a twice daily oral hydrocodone formulation which are within the OSLACK reference teaching. In this regard applicant may consider Example 19 and 20 which were compared to MS CONTIN (e.g. Example 19A). *It would appear to the Examiner that Examples 19 and 20, which the Examiner roughly calculated as having an @ C12/Cmax of .50 (2/4) and .61 (3.3/5.4) using the same Table and Figure used by applicant, would provide more guidance to one of ordinary skill in art* as to formulating OSLACK reference compositions (e.g. hydrocodone) which render obvious oral formulations "suitable for

twice a day administration" (e.g. Example 19) and/or anticipate (e.g. Example 20), respectively.

Applicant argues that Oshlack et al. fails to teach, hint or suggest the various pharmacological parameters recited in the presently claimed invention.

This argument is nonpersuasive for reasons already provided and for the following.

Applicant's argument is not commensurate to the presently claimed invention which encompasses any oral dosage formulation of hydrocodone with controlled release material which is "suitable for twice a day administration" and which possesses a given pharmacological profile. Accordingly, applicant's argument is clearly non-responsive to the above 102/103 rejection's assertion that the Oshlack reference anticipates or renders obvious hydrocodone formulations which due to their compositional components necessarily meets the presently claimed pharmacological profiles. In other words, the reference anticipates or renders obvious solid oral hydrocodone controlled-release formulations (or their manufacture) that comprise analgesically effective amounts of hydrocodone (or salt thereof) and which contain "controlled release material" which meet applicant's claimed pharmacological profile(s). Applicant has not rebutted this fact, nor has applicant attempted to make a comparison (declaration or otherwise) between the patented Oshlack compositions (NOT MS CONTIN which is NOT an Oshlack composition) and those compositions within the scope of the presently claimed invention. In this regard, the Oshlack disclosure, Examples and claims taken as a whole to one of ordinary skill in the art clearly

encompass "controlled release material " and active ingredients (e.g hydrocodone) "suitable for twice a day administration which are clearly within the scope of the presently claimed invention. It is noted that the Patent Office lacks the facilities to make comparisons between claimed and prior art compositions.

Applicant argues that the Oshlack patent's lack of an example, precludes inherent anticipation of the vaiously claimed pharmacokinetic paramters.

This argument was considered but deemed nonpersuasive since the patent claims (e.g. claim 6) anticipate, or in the alternative render obvious, [e.g. See e.g. *In re Schaumann*, 572 F.2d 312, 197 USPQ 5 (CCPA 1978); MPEP 2131.02; MPEP 2144.08)] hydrocodone formulations within the scope of the presently clamed invention but for inherent property (ies) which necessary result from compositions within the scope of the presently claimed invetion.

Applicant's cites *In re Rijckaert* as evidence that optimization somehow precludes anticipation. This argument is not persuasive for several reasons.

First, the In re Rijckaert court held with respect to an apparatus claim that prima facie obviousness was not met by the reference since parameters of the "time-base correction circuit" (.e.g "a' corresponding to the wrapping angle; "M" or "n") were not addressed by the reference thus precluding inherent anticipation.

The present case is clearly distinguishable from *Rijckaert*, since unlike the prior art in the Rijckaert case, the Oshlack patent clearly teaches composition components (e.g. solid oral dosage forms/hydrocodone/controlled release material) within the present claim scope **as well as pharmacokinetic paramaters** (e.g. disolution profiles:

once/twice day administration), including examples directed to opioid analgesic directed to additional pharmacokinetic profiles presently claimed including Tmax, Cmax etc. as well as the means to achieve (e.g. optimize) such pharmacokinetic values which are inherent to such resulting composition. Additionally, the Oshlack patent includes suitable "controlled release materials" include ammonio-methacrylate copolymers of acrylic/methacrylic acid esters having low content of quaternary ammonium groups (e.g. Eudragit RS and/or /RL as the "controlled release material") which corresponds to applicant's preferred embodiment.

Secondly, the case law recognizes time and again that "mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention". See In re Wiseman, 596 F.2d. 1019, 201 USPQ 658 (CCPA 1979). For granting a patent on the discovery of an unknown but inherent function "would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. See 201 USPQ at 661; In re Baxter, 952 F.2d 388, 21 USPQ2d 1281 (Fed. Cir. 1991).

It is again nothed that the patent office lacks the necessary facilities to make comparisons between prior art and presently claimed compositions. This is especially true regarding comparison between prior art compositions and those presently claimed dealing with the comparison of conventionally utilized pharmacokinetic parameters as in the present case. See e.g. *Purdue Pharma L.P. v. Boehringer Ingelheim GmbH* (DCSNY) 55 USPQ2d 168 (May 16, 2000) where pharmacokinetic paramaters (e.g.

including the same parameters as presently claimed) of an analgesic drug (e.g. Oxycontin) were determined by the (Oshlack) patentee for purposes of infringement.

Accordingly, the above 102/103 rejection is hereby maintained.

New Objection (s) and/or Rejection (s)

2. Claims 16-18, 20, 27, 33 and 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims have been amended to contain the trademark/trade name LORTAB . Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name LORTAB is used to identify/describe and, accordingly, the identification/description is indefinite.

Discussion

The above rejection was not addressed by applicant. Accordingly, it is hereby maintained.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bennett Celsa whose telephone number is 703-305-7556. The examiner can normally be reached on 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 703-306-3217. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Bennett Celsa
Primary Examiner
Art Unit 1639

BC
January 13, 2004